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REVIEW

A Network Meta-Analysis of Clinical Management Strategies for Treatment-Resistant Hypertension: Making Optimal Use of the Evidence

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BACKGROUND: With the addition of surgical interventions to current medicinal treatments, it is increasingly challenging for clinicians to rationally choose among the various options for treating patients with apparent treatment-resistant hypertension (ATRHTN).

This study aims to establish the comparative effectiveness of mineralocorticoid receptor antagonists (MRA), renal denervation (RDN), darusentan and central arteriovenous anastomosis (CAA) for patients with ATRHTN by performing a network meta-analysis.

METHODS:

Data Sources: Studies from recent meta-analyses for RDN and placebo effect were supplemented with a systematic search for MRAs in ATRHTN in the Pubmed, EMBASE, CINAHL and Cochrane databases through November 2016.

Study Selection: Randomized controlled trials comparing treatment options for patients with ATRHTN.

Data Extraction and Synthesis: Data were extracted using predefined data extraction forms, including the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. A Bayesian random effects model was used to conduct a network meta-analysis. Spironolactone was used as the main comparator.

Main Outcomes and Measures: Reduction in 24-h ambulatory blood pressure measurement (ABPM).

RESULTS: Twenty articles met our inclusion criteria, and seven treatment alternatives were compared. Compared to MRA, CAA had the highest probability of being more effective, further reducing 24-h SBP (−4.8 mmHg [−13.0, 3.7]) and 24-h DBP (−9.7 mmHg [−18, −0.63]). This difference is likely to be clinically meaningful, with a probability of 78 and 96% at a threshold of a 2-mmHg reduction in blood pressure.

CONCLUSIONS: When compared to MRA as anchor, darusentan, CAA and RDN are not more effective in achieving a clinically significant reduction in ambulatory blood pressure in individuals with apparent treatment-resistant hypertension.

KEY WORDS: treatment-resistant hypertension; network meta-analysis; MRAs.

J Gen Intern Med 32(8):921–30

DOI: 10.1007/s11606-017-4000-7

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INTRODUCTION

Hypertension (HTN) is the most common condition seen in primary care,¹ with a global prevalence of 41% in the general population.² Uncontrolled HTN is a risk factor for cardiovascular and renal disease, sources of significant morbidity and cost to society, and is therefore an important public health target.^{1,3,4} An estimated 14–16% of hypertensive patients have apparent treatment-resistant hypertension (ATRHTN).⁵ This proportion will be even higher if more stringent criteria are adopted for adequate blood pressure control.^{6–9} ATRHTN is defined as inadequately controlled blood pressure despite receiving three or more adequately dosed hypertensive medications, of which at least one is a diuretic.¹⁰ Adherence is a key factor in ATRHTN, and according to some estimates, 50% of patients with ATRHTN do not adhere to their medication.^{11–13}

The most common fourth-line treatment is the addition of a mineralocorticoid receptor antagonist (MRA) to the treatment regimen.¹⁴ In recent years, other pharmacological interventions have been developed, including darusentan,¹⁵ an endothelin receptor antagonist, as well as various device-based strategies such as renal denervation (RDN) and central arteriovenous anastomosis (CAA).¹⁶

A lack of data on the comparative effectiveness of these new treatment strategies poses challenges to the production and interpretation of relevant clinical evidence and to choosing optimal treatment strategies for patients. Direct comparison trials and conventional pairwise meta-analyses have demonstrated different conclusions regarding the efficacy of RDN, likely because of the heterogeneity in control treatments. Trials of RDN, for example, have compared RDN with standard medication therapy (no additional treatment),¹⁷ with a sham procedure (mimicking RDN without actually performing the intervention)¹⁸ and with MRA as add-on therapy.¹⁹ While a recent medium-sized trial showed that RDN was superior to

Electronic supplementary material The online version of this article (doi:10.1007/s11606-017-4000-7) contains supplementary material, which is available to authorized users.

Received October 21, 2016

Revised December 30, 2016

Accepted January 13, 2017

Published online March 8, 2017

MRA,¹⁹ another trial of the same size failed to show a difference in the primary endpoint.²⁰ Among direct comparisons of RDN with other active treatments, results have been mixed. Three conventional pairwise meta-analyses show RDN to be superior,^{17,21,22} while a fourth meta-analysis, based exclusively on randomized controlled trials (RCTs), casts doubt on these conclusions.²³

Conventional pairwise meta-analysis is unable to deal with heterogeneity in control interventions. A more appropriate approach in such cases is a network meta-analysis.²⁴ In a network-meta analysis, effect sizes associated with direct and indirect comparisons can be estimated for all treatment strategies in the network.²⁵ For example, in the case of ATRHTN, if trials have been reported comparing spironolactone (an MRA) with RDN and with darusentan, but no trials have been reported comparing darusentan to RDN directly, an indirect comparison can be made by using the results of the trials in which each was compared with darusentan.²⁵ Typically, all comparisons within a network meta-analysis are anchored to a placebo or to a widely accepted active comparator. Using this anchor, it is possible to determine the relative effects of any comparator in the network.

Network meta-analyses can be performed within a comparative effectiveness framework. The main question in this case is not simply whether a new therapy is effective, but whether it is substantially superior to the current standard of care. In the field of ATRHTN, guidelines recommend MRAs,²⁶ and therefore we consider this the most suitable anchor within this population.

The aim of this study is to use network meta-analysis to estimate the comparative effectiveness of the third-line hypertensive therapies darusentan, CAA and RDN, compared to a mineralocorticoid receptor antagonist anchor, in reducing systolic and diastolic blood pressure (SBP and DBP, respectively) in patients with ATRHTN.

METHODS

Study Identification and Data Extraction

The study was registered in the PROSPERO database, specifying the inclusion criteria and methods used²⁷ (PROSPERO 2015:CRD42015017323; available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015017323). To be included in the network meta-analysis, studies were required to meet the following criteria: 1) the study was an RCT; 2) treatment or control treatment were MRA, RDN or placebo (independent of active comparison); 3) the study population comprised patients with treatment-resistant hypertension, defined as uncontrolled hypertension despite receiving three or more antihypertensive medications, of which at least one is a diuretic; 4) the study was published in English; and 5) the study reported 24-h blood pressure obtained by ambulatory blood pressure measurement

(ABPM) for SBP and DBP outcomes (absolute or relative to baseline).

Pubmed, EMBASE, CINAHL and Cochrane databases were systematically searched for relevant articles in November 2016. The search terms and strategy are presented in detail in the Online Appendix. PM and KJ independently assessed titles and abstracts, and subsequently selected full-text articles. Records were assessed for eligibility and were excluded in the case of disease condition other than ATRHTN, studies not reporting primary clinical data, or case studies. In addition, two recent systematic reviews on MRAs,^{28,29} four recent meta-analyses of RDN^{17,21–23} and one meta-analysis on placebo effect in the ATRHTN population³⁰ were checked for relevant references. PM and KJ independently extracted relevant data using a pre-specified form. Main summary measures extracted were study characteristics and average 24-h ABPM. In addition, we extracted data on mean age, sex, study duration and inclusion criteria. Further outcomes extracted were office SBP and DBP (see Online Appendix). For all selected articles, PM and KJ assessed the risk of bias using the Cochrane risk of bias tool³¹ and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.³² All discrepancies between the coders were resolved by consensus.

Analysis

For the main analysis in the quantitative synthesis, we included studies reporting 24-h ABPM, and excluded studies reporting only office BPM. We have focused on 24-h ABPM, because high-quality evidence was available, and the measurement is more precise and reliable than office BPM. Office BPM was analyzed in a sensitivity analysis. We used a Bayesian random effects network meta-analysis approach to analyze the data, and meta-regression adapted for multiple treatment comparisons. Using meta-regressions, we controlled for the effect of differences in the previously identified variables baseline blood pressure and number of medications used.³⁰ Based on the search, the main treatment strategies assigned to the network nodes were: RDN, MRAs (spironolactone and eplerenone), placebo, sham, darusentan, CAA and regimens having more than 3 medications without an add-on. We relate SBP and DBP reduction to the minimum clinically important difference of 2 mmHg.³³

We used R version 3.3.1³⁴ for the analysis, specifically the GeMTC package version 0.8.1³⁵ for the meta-analysis.^{36,37} The network structure was generated using the `mtm.networkplot.fun` function in R.³⁸ We estimated heterogeneity across the network using I^2 . A value of I^2 below 40% was considered acceptable, while values above 75% were considered as evidence of considerable heterogeneity.³¹ Meta-regression was used to investigate the impact of imbalance in the covariates baseline blood pressure and number of co-medications used, in order to adjust for possible between-study confounders and intransitivity.²⁴ We also investigated inconsistency using a node-splitting approach.³⁹ Consistent

with the use of Bayesian analyses, we report 95% credibility intervals instead of confidence intervals. A 95% credibility interval signifies that there is a 95% probability that the true value lies between the lower and the upper bounds. Thus, our analysis allowed for estimation of the probability that a specific add-on treatment would result in a clinically important lowering of blood pressure in patients with ATRHTN compared to a specified alternative. Details on the estimation procedure are presented in the Online Appendix. Reporting is in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.^{40,41}

RESULTS

Study Selection, Characteristics and Risk of Bias

Database searches resulted in 1204 records, and 14 additional records were identified through cross-referencing of previously published meta-analyses (Figure A1). After the removal of duplicates, 984 unique records remained. Twenty studies met the inclusion criteria. Study characteristics are presented in Table 1. The 20 studies allowed comparison of ten medicinal or non-medicinal treatment strategies in the quantitative synthesis. Eplerenone and spironolactone were combined, and a single study with vitamin D was removed from the main analysis due to its ineffectiveness compared with placebo.⁴²

Figure A2 shows the risk of bias per study, while Figure A3 shows the risk of bias across studies, according to the GRADE criteria. The studies investigating device-based interventions in particular were not adequately blinded, lacking a sham-controlled study arm.

Results of Individual Studies

Table 2 shows the results of the individual studies. All treatments significantly reduced blood pressure compared to baseline values. This was also true for the control groups in 8 of the 19 studies, independently of whether an active comparator was used. The between-group difference in 24-h SBP reduction was statistically significant in all studies with the exception of Mathiassen,⁴⁶ Kario,⁴⁴ and SYMPPLICITY HTN-3.¹⁸ This difference was also clinically relevant (blood pressure reduction of 2 mmHg or more) in 13 of the 19 studies. In terms of DBP, there were significant differences in the majority of the studies, the exceptions being the studies by Mathiassen,⁴⁶ Kario,⁴⁴ Desch,⁴⁵ Azizi¹⁹ and Oxlund.⁴⁹ In 9 of the 19 studies, the between-group differences were clinically relevant.

Synthesis of the Results

The network structure is presented in Figure 1. All treatments were add-on therapies, offered to patients with ATRHTN in addition to three or more medications. The size of the circles represents the number of patients per alternative in the network; the lines between the circles show the direct comparisons in the network, with the thickness representing the total number of patients in the trials.

Figure 2 shows the results of the Bayesian random effects network meta-analysis for the 24-h SBP outcome. Since blood pressure reduction is the goal, negative numbers signify higher reduction versus the comparator, and positive values signify a relative increase in blood pressure. Figure 2a and b compares all strategies to spironolactone, with associated 95% credibility intervals (95% CrI).

Figure 3a and b shows the probability of a clinically relevant difference in blood pressure change compared to spironolactone for the 24-h DBP outcome. In Figure 3a and b, the curved lines signify the probability that the difference in blood pressure reduction is larger than the value indicated on the x-axis.

Effectiveness Compared to MRA. Compared to MRA, darusentan, CAA, and RDN were not more effective in lowering SBP in individuals with treatment-resistant hypertension. (Fig. 2a). The differences in SBP reduction between MRAs, RDN, darusentan and sham procedure were not clinically relevant. MRAs were significantly more effective than medication placebo (−13 mmHg [−9.9, −16.0]) and no additional treatment (−8.9 mmHg [−12.0, −5.7]), and these differences in SBP reduction were also clinically relevant. As shown in Figure 2c, the only treatment that had a reasonable probability of achieving a clinically relevant SBP reduction greater than MRAs was CAA (72%).

For DBP, CAA, Darusentan and RDN achieved significantly greater blood pressure reduction than MRAs (Fig. 2b). Conversely, the difference in DBP reduction due to spironolactone was not clinically relevant when compared with the reduction achieved by darusentan, RDN, and sham procedure. MRAs were significantly more effective than medication placebo −4.4 mmHg [−2.4, −6.5]) and no additional treatment −4.3 mmHg [−2.3, −6.1], and these differences were also clinically relevant. As can be seen on Figure 2d, CAA (92%) had a high probability of achieving a clinically relevant DBP reduction greater than MRAs.

Effectiveness Compared to Sham Procedure. Figure A4 shows the comparisons using the sham procedure as an anchor. For SBP, only RDN achieved a significantly greater reduction than the sham procedure. Conversely, the difference in SBP reduction due to the sham procedure was not clinically relevant when compared to darusentan. Sham procedures were more effective than medication placebo and no additional treatment, and these differences were clinically meaningful. As shown in Figure A4C, CAA (90%), RDN (82%) and MRAs (75%) had a reasonable probability of achieving a clinically relevant SBP reduction greater than sham. For DBP, only CAA achieved a significantly greater reduction than the sham procedure. The difference in DBP reduction due to the sham procedure was not clinically relevant when compared to darusentan, RDN and MRAs. Sham procedures were significantly more effective than medication and no additional treatment. As is evident from Figure A4D, CAA

Table 1 Overview of Included Studies and Their Characteristics, Ordered by Intervention

Study	Inclusion criterion	Method(s) of BP measurement	Intervention	Control	Follow-up (weeks)	Age in years, mean (SD)	Female, n (%)	Intervention group (n)	Control group (n)	BL 24-h SBP, mean (SD) mmHg	BL 24-h DBP, mean (SD) mmHg	BL office SBP, mean (SD) mmHg	BL office DBP, mean (SD) mmHg
Esler ⁴³	SBP > 160	Office BPM	Renal denervation	No additional treatment	24	58 (12)	45 (43%)	52 (20)*	53 (25)*	N/A	N/A	178 (17)	98 (16)
Kario ⁴⁴	SBP > 160	Office BPM	Renal denervation	No additional treatment	24	58 (6)	10 (24%)	22	19	164 (9)	N/A	180 (13)	93 (12)
Desch ⁴⁵	SBP > 135	24-h ABPM	Renal denervation	Sham	24	61 (4)	19 (27%)	35	36	140 (2.6)	79 (2.0)	N/A	N/A
Bhatt ¹⁸	SBP > 160	Office BPM	Renal denervation	Sham	24	57 (11)	210 (39%)	364	171	159 (13)	89 (14)	180 (16)	97 (16)
Mathiassen ⁴⁶	SBP > 145	Office BPM	Renal denervation	Sham	24	56 (9)	18 (26%)	36	33	152 (12)	90 (10)	163 (20)	93 (16)
Azizi ¹⁹	SBP > 140	Office BPM	Renal denervation	Spironolactone	24	55 (10)	40 (38%)	48	53	149 (16)	89 (14)	156 (22)	92 (15)
Rosa ²⁰	SBP > 140	Office BPM	Renal denervation	Spironolactone	24	57 (11)	29 (70%)	52	54	148 (12)	85 (10)	157 (18)	90 (14)
Oliveras ⁴⁷	SBP > 150	Office BPM	Renal denervation	Spironolactone	24	64 (7)	15 (63%)	11	13	153 (9)	81 (9)	156 (9)	84 (10)
Vaclavik ⁴⁸	SBP > 140	Office BPM	Spironolactone	Placebo	24	60 (10)	52 (35%)	55	56	143 (15)	82 (11)	154 (12)	92 (11)
Oxlund ⁴⁹	SBP > 130	Office BPM	Spironolactone	Placebo	16	63 (7)	28 (24%)	61	58	144 (10)	78 (7)	144 (15)	78 (10)
Ni ²⁰¹⁴ ⁵⁰	SBP > 140	24-h ABPM	Spironolactone	Placebo	12	55 (13)	31 (41%)	40	36	146 (11)	90 (13)	N/A	N/A
Bobrie ⁵¹	SBP > 135	Office BPM	Spironolactone	No additional treatment	12	56 (4)	41 (25%)	85	82	146 (14)	89 (10)	152 (20)	91 (11)
Yang ⁵²	SBP > 140	Office BPM	Spironolactone	No additional treatment	12	44 (13)	N/A	15	15	125 (12)	87 (7)	154 (11)	95 (12)
Black ⁵³	SBP > 140	Office BPM	Darusentan	Placebo	12	62 (10)	47 (41%)	76	39	137 (15)	77 (12)	149 (13)	81 (13)
Bakris ²⁰⁰⁷ ⁵⁴	SBP > 140	Office BPM	Darusentan	Placebo	14	62 (9)	217 (45%)	364	120	134 (15)	79 (11)	151 (11)	88 (10)
Weber ²⁰⁰⁹ ⁵⁵	SBP > 140	Office BPM	Darusentan	Placebo	14	62 (9)	191 (52%)	247	132	135 (14)	78 (10)	151 (11)	87 (11)
Karns ²⁰¹² ⁵⁶	SBP > 140	Office BPM	Eplerenone	Placebo	8	58 (9)	25 (38%)	33	33	N/A	N/A	154 (9)	90 (11)
Eguchi ²⁰¹⁶ ⁵⁷	SBP > 135	Office BPM	Eplerenone	No additional treatment	12	62 (12)	28 37%	40	36	135 (10)	68 (7)	145 (14)	78 (10)
Lobo ²⁰¹⁵ ⁵⁸	SBP > 140	Office BPM	Central arteriovenous anastomosis	No additional treatment	24	59 (9)	25 (30%)	44	39	157 (14)	93 (12)	173 (13)	100 (9)

Abbreviations: BP blood pressure, BL baseline, SBP systolic blood pressure, DBP diastolic blood pressure, SD standard deviation, BPM blood pressure measurement, ABPM ambulatory blood pressure measurement

* stands for: patients with 24-h blood pressure measurements

Table 2 Treatment Effects in Studies Reporting 24-h ABP Measurements

Study		Mean (95% CI) change from BL 24-h SBP mmHg	Mean (95% CI) difference between groups 24-h SBP mmHg	Mean (95% CI) change from BL 24-h DBP mmHg	Mean (95% CI) difference between groups 24-h DBP mmHg	
Esler 2010 ⁴³	Treatment Control	Renal denervation No additional treatment	-11 (-15.2, -6.8) -3.0 (-8.2, 2.2)	-8.0 (-11.4, -4.6)	-7.0 (-10.1, -3.9) -1.0 (-4.3, 2.3)	-6.0 (-8.3, -3.7)
Kario 2015 ⁴⁴	Treatment Control	Renal denervation No additional treatment	-7.5 (-19.5, 4.5) -1.4 (-11.6, 8.8)	-6.2 (-13.2, 0.9)	-4.2 (3.2, -11.6) -0.4 (-7.1, 6.3)	-3.8 (-8.3, 0.6)
Bhatt 2014 ¹⁸	Treatment Control	Renal denervation Sham	-6.8 (-8.3, -5.2) -4.8 (-7.4, -2.2)	-2.0 (-5.0, 1.0)	-4.1 (-5.1, -3.1) -3.1 (-4.6, -1.6)	-1.0 (-1.9, -0.1)
Desch 2015 ⁴⁵	Treatment Control	Renal denervation Sham	-7.0 (-10.8, -3.2) -3.5 (-6.7, -0.2)	-3.5 (-4.4, -2.7)	-2.8 (-4.8, -0.9) -2.1 (-3.9, -0.2)	-0.7 (-1.2, -0.3)
Mathiassen 2016 ⁴⁶	Treatment Control	Renal denervation Sham	-3.7 (-20.1, 12.7)	1.1 (-5.9, 8.1)	-1.7 (-10.3, 6.9)	0.9 (-2.8, 4.6)
Rosa 2015 ²⁰	Treatment Control	Renal denervation Sham	-2.6 (-15.4, 10.2) -8.6 (-11.8, -5.3)	-0.5 (-6.1, 5.2)	-2.6 (-10.1, 4.9) -5.7 (-7.9, -3.4)	-1.7 (-4.3, 2)
Azizi 2015 ¹⁹	Treatment Control	Spirolonactone Renal denervation	-8.1 (-12.7, -3.4) -15.4 (-19.1, -11.7)	-5.9 (-11.0, -0.1)	-4.5 (-6.8, -2.3) -9.7 (-12, -7.0)	-3.1 (-6.3, 0.1)
Oliveras 2016 ⁴⁷	Treatment Control	Spirolonactone Renal denervation	-9.5 (-13.0, -6.0) -5.7 (-14.8, 3.4)	-17.9 (-30.9, -4.9)	-6.6 (-8.8, -4.4) -3.7 (-8.2, 0.9)	-6.6 (-12.9, -0.3)
Vaclavik 2014 ⁴⁸	Treatment Control	Spirolonactone Placebo	-23.6 (-31.9, -15.3) -12.6 (-15.2, 10.0)	-10.5 (-14.6, -6.3)	-10.2 (-14.4 to -6.1) -5.0 (-7.2, -3.8)	-3.5 (-5.9, -1.0)
Oxlund 2013 ⁴⁹	Treatment Control	Spirolonactone Placebo	-2.1 (-2.3, -1.9) -9.7 (-13.0, -6.4)	-8.9 (-13.2, -4.6)	-2.0 (-3.8, -0.3) -4.2 (-5.8, -2.6)	-3.9 (-6.2, 1.7)
Bobrie 2012 ⁵¹	Treatment Control	Spirolonactone No additional treatment	-0.8 (-3.6, 2.1) -17.0 (-19.2, -14.8) -7.0 (-9.2, -4.8)	-10 (-14.0, -6.0)	-0.3 (-1.9, 1.3) -10.0 (-11.4, -8.6) -6.0 (-7.3, -4.6)	-4.0 (-6, -2)
Ni 2014 ⁵⁰	Treatment Control	Spirolonactone Placebo	-11.5 (-19.1, -3.9) 0.5 (-6.4, 7.4)	-12.5 (-13.8, -11.2)	-7.5 (-14.6, -0.4) -1.5 (-9.6, 6.6)	-7.0 (-8.6 to -5.4)
Yang 2016 ⁵²	Treatment Control	Spirolonactone No additional treatment	-16.3 (-26.3, -6.3) -5.3 (-12.3, 1.7)	-11 (-14.2, -7.8)	-14.9 (-23.3, -6.5) -2.9 (-9.2, 3.4)	-12 (-14.7, -11.3)
Kams 2013 ⁵⁵	Treatment Control	Eplerenone Placebo	N/A N/A	-14.7 (-23.1, -6.3)	N/A N/A	-9.7 (-15.2, -4.2)
Eguchi 2016 ⁵⁶	Treatment Control	Eplerenone No additional treatment	-3 (N/A) 2 (N/A)	-5 (-11.2, 1.2)	-2.5 (N/A) 1.5 (N/A)	-4 (-7.4, -0.6)
Black 2007 ¹⁵	Treatment Control	Darusentan Placebo	N/A N/A	-9.2 (-11.4, -7.0)	N/A N/A	-7.2 (-8.8, -5.6)
Bakris 2010 ⁵³	Treatment Control	Darusentan Placebo	-9.0 (-21.0, 3.0) -2.0 (-14.0, 10.0)	-7.0 (-8.3, -5.7)	-7.5 (-8, -7) -1.5 (-2.5, -0.5)	-6.0 (-6.07, -5.9)
Weber 2009 ⁵⁴	Treatment Control	Darusentan Placebo	-17.0 (-20.6, -13.4) -8.1 (-12.7, -3.4)	-9.0 (-11.1, -6.9)	-10.0 (-12.1, -7.9) -5.0 (-6.7, -3.6)	-5.0 (-6.2, -3.8)
Lobo 2015 ¹⁶	Treatment Control	arteriovenous anastomosis No additional treatment	-13.5 (-32, 5) -0.5 (-17, 12)	-13.0 (-20.5, -5.5)	-13.5 (-22.0, -6.0) -0.1 (-10.0, 10.0)	-13.8 (-22.6, -5.3)

CI credibility interval, BL baseline

Network of Eligible Comparisons in Treatment Resistant Hypertension

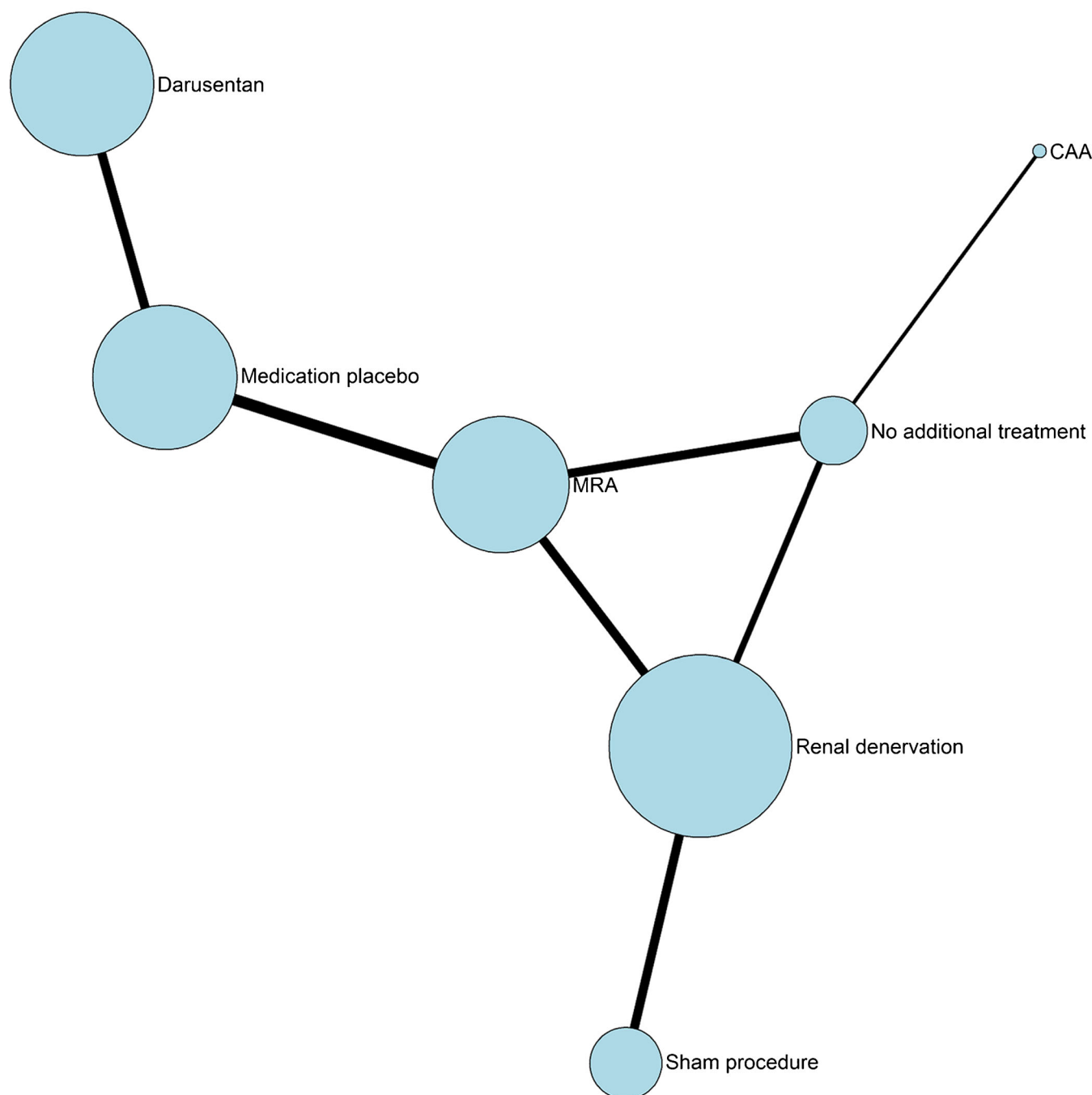


Figure 1 Network structure of studies with available 24-h ABPM.

(98%) had a reasonable probability of achieving a clinically relevant DBP reduction greater than the sham procedure.

Risk of Bias Across Studies and Additional Analyses

Heterogeneity in the study results was moderate, with $I^2 = 52.7\%$ for SBP and $I^2 = 44.2\%$ for DBP. The inclusion of baseline covariates such as baseline blood pressure and number of medications used did not significantly impact the results

of the meta-analysis, nor could they account for the observed heterogeneity. No evidence of publication bias was found. Office SBP and DBP point estimates were broadly similar to the 24-h ABPM results, with the exception of the CAA and sham procedure results, and the uncertainty around these estimates was much higher. Compared to the use of 24-h SBP/DBP measurements as outcomes, a network meta-analysis of office measurements resulted in a higher level of heterogeneity ($I^2 = 61.2\%$ for OSBP and $I^2 = 99\%$ for ODBP respectively). A sensitivity analysis, discarding studies with

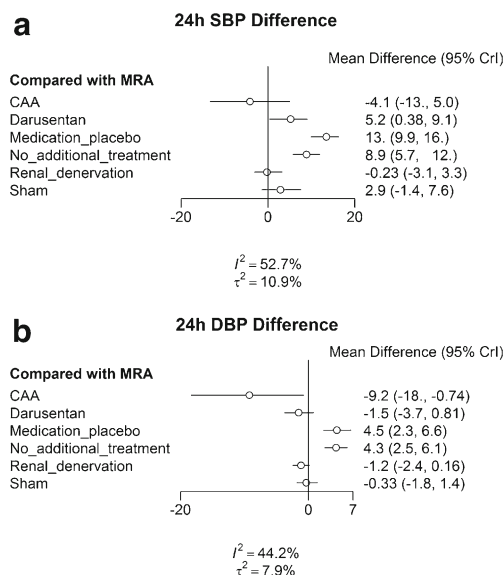


Figure 2 Estimated differences in mean 24-h SBP and DBP (mmHg) reductions, including 95% credibility intervals (CrI). **a** Effectiveness of the various treatment options on the SBP outcome compared to MRA. **b** Effectiveness of the various treatment options on the DBP outcome compared to MRA.

more than three indicators of bias, did not produce results that differed from the main analysis.

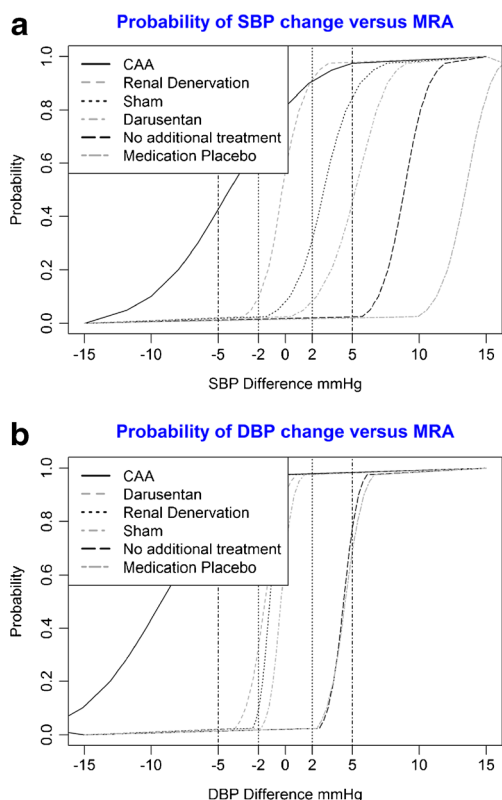


Figure 3 Probability of blood pressure change at various minimum clinically important difference levels. **a** Probability of SBP change versus MRA at various minimum clinically important difference levels. **b** Probability of DBP change versus MRA at various minimum clinically important difference levels.

DISCUSSION

Summary of Evidence

Comparative Effectiveness. When compared to MRA as an anchor, darusentan, CAA and RDN were not more effective in achieving a clinically significant reduction in ambulatory blood pressure measurement in individuals with ATRHTN. Most individual comparative trials testing a specific medical or non-medical regimen in patients with treatment-resistant hypertension have reported some, albeit variable, benefit in terms of blood pressure control. However, the use of different comparators, including no additional treatment, drug placebo, sham procedure and active comparator, hampers the interpretation of results across studies. Conventional meta-analyses to date have been unable to resolve this problem, because by lumping of control interventions, they ignore the heterogeneity of the comparators.^{17,21,22} A network meta-analysis can accommodate this type of heterogeneity,²⁴ enabling optimal use of the available evidence to guide clinical management. The results of such an approach here show that none of the treatments included in this study resulted in a statistically significant greater SBP reduction compared with MRAs. For DBP, CAA resulted in a clinically relevant and statistically significant greater reduction. The results also allow for an estimate of the probability that either of these treatments result in clinically relevant better blood pressure control. For 24-h SBP, CAA has a 72% probability of resulting in better BP control than MRAs. For 24-h DBP, this figure is 98%. With such figures, individual clinicians and guideline committees can weigh the probability of successful treatment against potential side effects or cost-effectiveness in order to select optimal treatments for patients with treatment-resistant hypertension. An additional advantage of this type of analysis is that such results might be interpreted more easily by patients, facilitating patient-physician communication.

Effectiveness Compared to Placebo. Particular care needs to be taken in interpreting the effectiveness of the interventions, as significant and major differences were found between medication placebo and sham procedure, another type of placebo. Compared with medication placebo or no additional treatment, MRAs significantly reduced both SBP and DBP. The magnitude and the significance of the medication placebo adjusted effect was similar to that in a recent study using home blood pressure outcome measurement,⁵⁷ and in line with the effects found in recent meta-analyses.^{29,58} At the same time, the effects of MRAs on SBP reduction did not differ from the effects of a sham procedure, another kind of placebo. While this may sound counterintuitive, these results are consistent with the literature as far as the difference in effect size between sham procedures and medication placebo both in this population and in general,^{30,59,60} while both have a marked effect on blood pressure reduction.³⁰ It is possible that the enhanced clinical routine⁶¹ surrounding a sham procedure increases adherence to the background medications in these patients.

While it is likely that adherence to medication also improves somewhat under trial conditions, such increased adherence is less likely when an additional medication is introduced to an already busy medication schedule of four chronic medications on average. In any case, it seems appropriate to use a sham procedure as an effectiveness benchmark in ATRHTN for future interventions, as it appears to provide a common benchmark for comparing both medication and device-based treatment strategies.

Limitations

This review is not comprehensive, as it does not include all possible treatments for ATRHTN, because not all treatment strategies reported 24-h ABPM for the main analysis. We have focused on 24-h ABPM, for which high-quality evidence was available. In the overall GRADE assessment for the 24-h SBP and DBP outcomes, we have not downgraded the studies, and the quality of the evidence remains high. Using GRADE, results for the office SBP/DBP outcome were downgraded mainly due to imprecision and inconsistency (heterogeneity) across studies. This imprecision may be due to the fact that office blood pressure values are not particularly reliable, and are prone to be influenced by white-coat effects.³⁰ In addition, inconsistency (heterogeneity) in office SBP and DBP was substantial or considerable,³¹ leading to unreliable conclusions. As a result, treatments reporting only office blood pressure were excluded. Therefore, barostimulation therapy could not be compared in the main analysis, nor could we include the alpha blocker doxazosin or the beta blocker bisoprolol reported in the recent PATHWAY-2 study.⁵⁷ At the same time, we are confident that we have been able to include all relevant studies reporting 24-h ABPM on MRAs, RDN and particularly placebo-controlled studies on any treatment strategy³⁰ in the ATRHTN group, and were thus able to make indirect comparisons between these major strategies for the treatment of ATRHTN.

More importantly, we could not determine whether the patients in the individual studies were truly adherent to three or more antihypertensive medications. This is an important limitation, as there is evidence suggesting that only half of all ATRHTN patients fall into the true ATRHTN category, while the other half may have been misdiagnosed because they did not fully adhere to medication.^{11–13} Furthermore, non-adherence cannot be reliably measured in this population using self-reported questionnaires,⁶² requiring urine tests to monitor adherence.¹¹ This may explain why MRAs are not notably more effective than sham. While it is likely that adherence to medication increases during trial conditions, it is also likely that 100% adherence is not obtained, which may lead to an underestimation of the treatment effect of MRA—and all other add-on medication. Consequently, the results may be driven in part by improved adherence rather than the true effect of an additional medication.

Another limitation of this network meta-analysis was the variation in the patient populations among studies, which

could have influenced the results. We adjusted for possible sources of heterogeneity between studies²⁴ using previously identified variables such as baseline blood pressure and number of co-medications used,³⁰ and the results were not sensitive to these variables. However, because of the low number of studies and the association between covariate levels and treatment strategies, we were not able to use multivariable adjustment techniques in the meta-regression.

In addition, there was substantial use of spironolactone in both the treatment and control arms of trials that did not evaluate mineralocorticoid receptor antagonist-based therapies. For example, mineralocorticoid receptor antagonists were used in 22–28% of patients in the SYMPLICITY HTN-3 trial, 17% in the SYMPLICITY HTN-2 trial, and 37–45% of patients in the SYMPLICITY HTN-Japan trial. This contributes to treatment cross-contamination of comparator groups for the indirect pooled comparison of mineralocorticoid receptor antagonists with other groups, and may bias the results towards the null. At the same time, the two moderately large direct comparisons^{19,20} showed that there was indeed a small difference between the two treatment alternatives, with only the third, very small study ($n = 24$) showing larger differences.⁴⁷

In terms of network consistency, no significant inconsistency was found in the RDN–spironolactone–no additional treatment loop. However, a major limitation of this study is that for most comparisons, there was no combination of direct and indirect evidence: the network contained only a single closed loop enabling comparison of direct and indirect treatments. Therefore, we were only partially able to investigate the consistency of the results; this can be performed fully only if additional trials are reported directly comparing various treatment strategies in the network, thus closing the network's loops.

CONCLUSIONS

Implications for Practice

The only alternative to MRAs which achieved a clinically meaningful blood pressure reduction of 2 mmHg with high probability was CAA. However, the results of CAA are based on a single study, and thus should be interpreted with caution. Also, CAA has frequent adverse effects; therefore, it may not be useful in practice. RDN and darusentan were not clinically different from MRAs.

Implications for Research

Because inconsistency within the network could only be partially assessed, evidence in the field of ATRHTN would benefit from more direct comparisons of various treatments options, particularly in the case of CAA. In order to improve comparability between strategies, 24-h ABPM should be used in such studies, and adherence should be closely monitored to

ensure that only true treatment-resistant hypertension patients are included in the trials.

Acknowledgements: We would like to thank Janneke Grutters for her useful comments on a previous version of this paper. We also thank Alice Tillema for her help in updating the search.

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Compliance with Ethical Standards:

Conflict of interest: The authors declare no conflict of interest.

Funding: No external funding was received for this manuscript.

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